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Synthetic enhanced EP delivered Ig plasmid vector drives biologically relevant anti-HIV-1 envelope responses *in vivo*

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Background: Monoclonal Ab's have demonstrated therapeutic utility against several malignancies and infectious diseases. A drawback of this strategy is the time-consuming and expensive process requiring purification and scale up production of the Ab's for clinical use. A method to produce antibodies *in vivo* would be significant improvement for this platform. It would be important if these Ab's could be administered without induction of vector serology allowing repeated administrations. Furthermore, delivery in a non-permanent fashion would also have advantages.

Methods: Here we report development of new synthetic optimized plasmid vector/improved EP encoding Abs genes for delivery *in vivo*. This strategy allows for *in vivo* synthesis and serum expression of such ex vivo developed antibodies. The antibodies were found to be expressed in the blood as well as in other compartments and were functional and at protective levels for model systems.

Results: An "enhanced and optimized" DNA plasmid generates immunoglobulin heavy and light chains (Fab) of an established neutralizing anti-HIV monoclonal antibody (VRC01). We demonstrate that the serum of transfected animals exhibited the ability to bind to HIV envelopes in ELISA and FACS analysis against diverse isolates and this serum possessed HIV neutralizing activity equivalent to the "native" VRC01 antibody in vivo. *In vivo* delivery sero converted the animals within a few hours and neutralizing activity lasted for weeks. This technology has important advantages for in vivo antibody production which could compliment or circumvent the need for standard antigen based vaccination, particularly in situations where there is difficulty in generation of protective antibody responses by immunization.

Conclusion: This is the first study we are aware of using synthetic DNA plus EP delivery to produce circulating bioactive antibody responses in a living animal. The study has implications for prophylactic and therapeutic strategies for HIV and other important diseases.

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